Human Thermoregulation After Atropine and/or Pralidoxime Administration

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The effects of intramuscular saline (control), atropine (2 mg), and/or pralidoxime (600 mg) on heat exchange was evaluated in four healthy males during seated, cycle exercise (55% Vo_2 peak) in a temperate environment (T_a = 30.3°C, P_w = 4.0 kPa). Esophageal (T_{es}), rectal (T_{re}), and mean skin temperatures (T_{sk}), and chest and forearm sweating (m_s) were continuously measured. Skin blood flow (FBF) from the forearm was measured twice each minute by venous occlusion plethysmography. Whole body sweating was calculated from weight changes. The expected result of atropine injection, decreased eccrine sweating (−60%, $p<0.05$) and elevated esophageal (+0.4°C, $p<0.05$) and skin temperatures (+2.4°C, $p<0.05$) was observed relative to control. Heart rate (+28 b·min^{-1}) and FBF (+9 ml·100ml^{-1}·min^{-1}) were higher after atropine. Pralidoxime, in general, did not affect the core and skin temperature responses to the exercise differently from control; however, a slightly elevated FBF (+3ml·100cc^{-1}·min^{-1}, 33%) compensated for the reduction in whole body sweating (−45%, $p<0.05$)) that we observed. The combination of the drugs resulted in significantly higher esophageal (0.4°C) and skin (0.9°C) temperatures than atropine alone, as has been previously shown. The thermoregulatory disadvantage of inhibited sweating by atropine was partially compensated for by enhanced skin blood flow in this environment where $T_a<T_{sk}$. Pralidoxime was shown to decrease whole body sweating, by a mechanism as yet unexplained.

ECCRINE SWEAT GLAND activity is depressed by systemic or local atropine administration through competitive inhibition of cholinergic receptors (1,9,14) resulting in reduced evaporative heat loss (40–60%) in adult males (1,9,13). A cutaneous "atropine flush" accompanies these inhibitory effects on the sweat gland (4), but whether the "flush" is an active mode of heat exchange has not been elucidated. We (5) and others (3) have estimated higher cutaneous blood flow after atropine by calculating enhanced dry heat loss. However, the measurement of cutaneous blood flow by venous occlusion plethysmography or other methods after whole body atropine administration has not been undertaken.

Pralidoxime chloride (2PAM) is currently used as an antidote to organophosphate poisoning. The action of 2PAM centers around the reactivation of bound acetylcholinesterase for the hydrolysis of acetylcholine to enable synapses to function normally (6). In the absence of impaired enzyme, the action of 2PAM is not clear. When given in therapeutic doses (600 mg, i.m), 2PAM caused no changes in core temperature, skin temperature, heart rate, or whole body sweating rate in resting men at 40.5°C, 1.5 kPa (13). After oral 2PAM administration (2), there were no changes in core or skin temperature during low intensity exercise at 19, 29, 38, or 46°C. However, whole body sweating was reduced an average of 10% in these studies. Transient hypertension occurs following 2PAM treatment (6), and in the presence of a higher sympathetic drive (exercise or combat), sudden and dramatic increases in precapillary vascular resistance (therefore elevating blood pressure) may occur in individuals treated with pralidoxime chloride with appropriate changes in peripheral blood flow and heat dissipation. Additionally, systemic administration of 2PAM and atropine point to an augmentation of the atropine-induced rise in body temperature in the presence of 2PAM (2).

In the present study, we were interested in ascertaining

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the individual and combined actions of atropine and pralidoxime on thermoregulatory sweating and vasodilation in healthy males during moderate intensity exercise in a temperate environment.

METHODS

Subjects. Four fit males ($\dot{V}O_2$ peak 46 ml·kg^{-1}·min^{-1}) volunteered for the study following consent procedures passed by our local Human Use Committee. They had an average (±S.D.) age of 21 ± 2 yrs, height of 182 ± 9.1 cm, weight of 81.3 ± 9.8 kg, DuBois surface area of 2.03 ± 0.16 m^2, percentage of body fat (hydrostatic weighing) of 18.7 ± 4.4%, and a lean body mass of 66.1 ± 3.6 kg.

Protocol. Testing occurred during November 1985. All subjects were familiarized with all testing and measurement procedures before data collection began. Subjects were tested on 4 separate days in an ambient temperature of 30°C with an ambient water vapor pressure (P_w) = 1.0 kPa. Testing occurred after injection (im) of sterile saline, 2 mg of atropine sulfate (Elkin-Sinn, Cherry Hill, NJ), 600 mg pralidoxime chloride (protopam chloride, Ayerst, NY, NY) or 2 mg atropine plus 600 mg pralidoxime chloride. Subjects were not aware of the drug(s) being injected. Test days were separated by 48 h, and the order of drug presentation was counterbalanced. Experiments were conducted between 0700 and 1000 hours, with any one subject tested at the same time each day to control for circadian variation in heat loss responses (15). Subjects had fasted 12 h before testing.

Physiological variables. The seated exercise level was 55% of a previously determined $\dot{V}O_2$ peak on a modified cycle ergometer (11). Total exposure time was 80 min, which included a 5-min baseline period after instrumentation and equilibration, the injection of the appropriate drug, 30 min of rest, 30 min of submaximal exercise, and a 15-min recovery period. We continuously recorded esophageal temperature (T_{es}), rectal temperature (T_{re}), an eight-site, mean-weighted skin temperature ($\bar{T}_{sk}$) (12), and sweating rate (7) from the chest ($\dot{m}_{sch}$) and forearm ($\dot{m}_{sa}$). Heart rate (HR) measured from electrocardiogram and blood pressure (automatic auscultation) were measured each 2.5 min. Forearm blood flow (FBF) was measured twice each min by venous occlusion plethysmography (8,16) on the contralateral forearm from which blood pressure was measured. Metabolic heat production was estimated by open circuit spirometry at 15 minutes of rest, 10 minutes of exercise, 25 minutes of exercise and at 5 minutes of recovery. Total body sweating rate (g·min^{-1}) was determined by pre- and post-experiment weights of the nude body.

Statistical Analysis. Analysis of variance routines were used to compare all variables at the time of the metabolic heat production measurements (rest, 10 and 25 min of exercise, and 5 min of recovery). Regression equations of both internal temperature measurements over time were generated to calculate the rate of change in

TABLE I. MEAN (±S.D.) TEMPERATURE PARAMETERS FOR THE FOUR SUBJECTS DURING THE FOUR TREATMENTS AT REST, DURING EXERCISE, AND RECOVERY.

	T_{es} (°C)	T_{re} (°C)	$\bar{T}_{sk}$ (°C)	FBF (ml·100ml^{-1}·min^{-1})	Arm $\dot{m}_s$ (mg·cm^{-2}·min^{-1})	Chest $\dot{m}_s$ (mg·cm^{-2}·min^{-1})	$\dot{M}_s$ (g·min^{-1})	Heart Rate (b·min^{-1})
Saline								
Rest	36.67(.15)	37.17(.25)	34.04(.28)	1.84(.83)	0.16(.06)	0.31(.35)		67(8)
Exercise 1	37.15(.14)	37.27(.22)	33.32(.59)	6.09(.87)	0.97(.17)	1.43(.31)		127(4)
Exercise 2	37.37(.15)	37.64(.15)	33.62(.51)	9.21(.42)	1.08(.30)	1.78(.61)		130(5)
Recovery	37.01(.36)	37.76(.16)	33.64(.50)	5.55(.76)	0.74(.38)	1.78(.87)	13.23(3.68)	87(10)
Atropine								
Rest	36.61(.20)	37.06(.20)	34.06(.30)	1.84(0.45)	0.15(.04)	0.23(.28)		59(13)
Exercise 1	37.08(.18)	37.13(.15)	34.92(.48)*	11.04(3.08)*	0.35(.20)*	0.33(.34)*		146(11)*
Exercise 2	37.78(.18)*	37.62(.14)	35.72(.49)*	17.08(5.78)*	0.43(.14)*	0.61(.28)*		158(4)*
Recovery	37.80(.22)*	37.97(.11)*	36.03(.35)*	15.04(8.01)*	0.45(.17)*	0.67(.36)*	5.53(1.37)*	142(13)*
Pralidoxime								
Rest	36.48(.30)	36.92(.28)	33.97(.54)	1.93(0.94)	0.12(.01)	0.12(.02)		66(12)
Exercise 1	37.00(.29)	37.14(.25)	33.76(.54)*†	9.13(4.13)	1.14(.32)	1.47(.33)		126(11)
Exercise 2	37.16(.25)†	37.56(.22)	33.95(.80)†	12.26(4.20)†	1.41(.21)*	1.67(.39)		123(12)
Recovery	36.98(.21)†	37.66(.19)	33.80(.73)†	5.34(1.82)†	0.72(.43)	1.44(.80)*	7.03(2.16)*	93(23)
Combination								
Rest	36.76(.28)	37.11(.23)	33.97(.64)	1.35(0.29)	0.16(.04)	0.34(.30)		71(11)
Exercise 1	37.32(.25)	37.24(.20)	35.34(.65)*‡	12.64(1.74)*	0.35(.24)	0.26(.14)*		139(6)*
Exercise 2	38.18(.27)*‡	37.83(.28)	36.40(.57)*‡	17.36(4.63)*‡	0.45(.18)	0.45(.16)*		155(2)*
Recovery	38.28(.21)*‡	38.29(.27)	36.71(.29)*‡	16.31(2.12)*‡	0.40(.21)*	0.95(.30)*	5.35(2.91)*	157(14)*

*Different from saline ($p<0.05$)
†Different from atropine ($p<0.05$)
‡Different from pralidoxime ($p<0.05$)

heat content. Tukey's test of critical differences was used where appropriate. All differences are reported at $p<0.05$, unless otherwise noted.

RESULTS

There were no statistically significant differences in any of the resting variables for any of the four drug treatments. Furthermore, there was no treatment effect on the metabolic heat production or mean arterial pressure during exercise which averaged 351 $W \cdot m^{-2}$ and 104 mm Hg, respectively. Mean heat exchange information is presented in Table I for the four subjects under all testing conditions. As expected, atropine elevated heart rates during exercise (22%) and recovery (62%) over those rates seen in control experiments with pralidoxime not affecting exercise heart rate. The combination of atropine and pralidoxime increased exercise (19%) and recovery (80%) heart rates. Depressed local and whole body sweating (arm, −64%; chest, −77%; whole body, −58%) occurred with atropine as did the expected rise in both core and mean weighted skin temperatures. FBF was elevated following atropine; 83% during exercise and 170% during recovery. Pralidoxime injection, in general, did not affect rest, exercise, or recovery values for T_{re}, T_{es}, or $\bar{T}_{sk}$. However, FBF was slightly elevated (+3.0 $ml \cdot 100ml^{-1} \cdot min^{-1}$; 33%, NS), and whole body sweating (−6.2 $g \cdot min^{-1}$, −47%) and recovery chest sweating (−0.48$mg \cdot cm^{-2} \cdot min^{-1}$) were reduced. The combination of atropine and pralidoxime resulted in higher T_{es} (0.4°C) and $\bar{T}_{sk}$ (0.7°C) than atropine itself during the 25th min of exercise. FBF, whole body and local sweating were not different from the atropine treatment.

The rate of increase (dT/dt) for esophageal and rectal temperature is shown in Table II for all subjects during all treatments. As expected, dT_{es}/dt was higher than dT_{re}/dt in all cases. In addition, dT_{es}/dt was significantly affected by all treatments, whereas dT_{re}/dt was affected only by the combination of drugs. A graphic representation of the two temperatures over time is shown in Fig. 1 for a single subject during both saline and atropine experiments.

DISCUSSION

This investigation provides initial evidence that systemic atropine administration alters peripheral heat loss, not only via depressed thermoregulatory sweating, but also through elevated skin blood flow. Additionally, pralidoxime administration results in a depressed whole body sweating response without affecting core and skin temperature regulation in a temperate environment

TABLE II. INDIVIDUAL AND MEAN (±S.D.) dT/dt (°C·min^{-1}) FOR ESOPHAGEAL AND RECTAL TEMPERATURES DURING EXERCISE TRANSIENTS FOR THE FOUR TREATMENTS.

Treatment	Temperature	
	Esophageal	Rectal
Saline		
S_1	.08779	.04060
S_2	.09360	.02349
S_3	.06259	.02232
S_4	.06823	.01899
	.0781 (.0150)	.0264 (.0097)
Atropine		
S_1	.07400	.04059
S_2	.07669	.02273
S_3	.05310	.02810
S_4	.0604	.03111
	.0660 (.0112)*	.0306 (.0075)
Pralidoxime		
S_1	.07909	.05701
S_2	.10814	.03067
S_3	.08648	.02030
S_4	.08187	.02423
	.0889 (.0132)*†	.0331 (.0165)
Combination		
S_1	.08605	.04387
S_2	.06235	.04336
S_3	.05352	.03851
S_4	.05195	.03707
	.0635 (.0157)*‡	.0407 (.0034)*†‡

S_1 through S_4 are subject numbers.
*Different from saline ($p<0.05$)
†Different from atropine ($p<0.05$)
‡Different from pralidoxime ($p<0.05$)

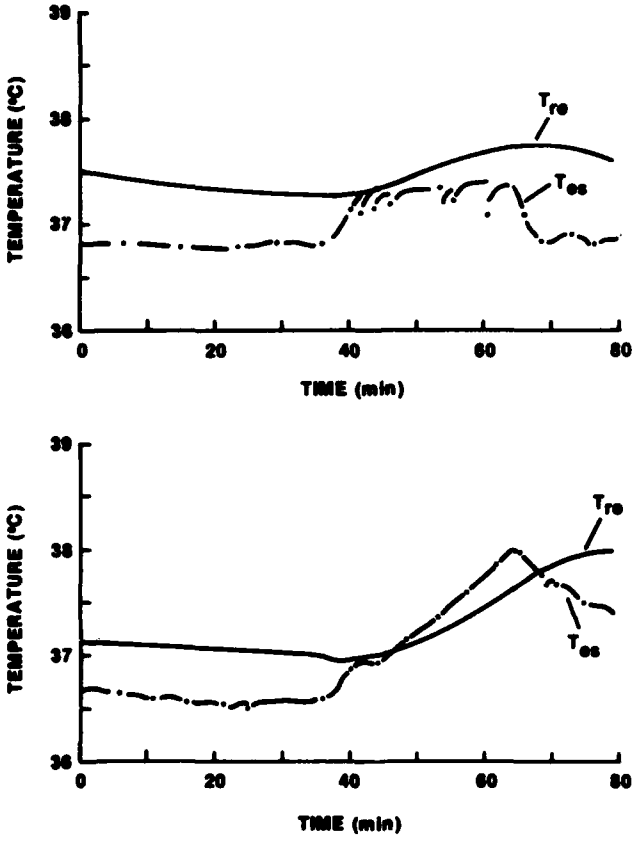

Fig. 1. The time course for both esophageal and rectal temperature for one subject after saline (upper panel) and atropine (lower panel). The drug is injected at 5 min, exercise begins at 35 min, and recovery begins at 65 min.

during moderate intensity exercise. The combination of the two drugs, in general, confirms the potentiation of impaired heat exchange that has been reported previously (2).

The depression in thermoregulatory sweating seen following atropine was expected (1,9), and was of the same magnitude as previously reported for unacclimated subjects (9). The compensation for reduced evaporative heat loss from the skin, which occurs via skin blood flow has been suggested (3,5) and may in part explain the atropine flush which is usually observed (4). This elevation in skin blood flow appears to be a result of an enhanced sensitivity to the increasing esophageal temperature drive (10).

The responses of the subjects after the pralidoxime injection were not completely expected. One response which appears equivocal is the depression in whole body sweating (Table II). Smaller decreases in whole body sweating were demonstrated previously (2), but no record of this level of inhibition is available. Paradoxically, local sweating was not depressed by the pralidoxime treatment, perhaps indicating a differential effect of the inhibition of sweat secretion at different locations. Since T_{es} and $\bar{T}_{sk}$ were not different after pralidoxime injection compared to saline treatment (Table II), the slight enhancement in FBF resulting in further sensible heat loss together with the regulatory sweating observed was sufficient for whole body heat dissipation. In environments where $T_a \geq \bar{T}_{sk}$ heat dissipation would be compromised during pralidoxime treatment due to inhibited sensible heat exchange by the environmental gradient as well as by inhibited evaporation. The enhancement in skin blood flow is contrary to what we expected, since transiently increased vascular resistance has been seen after pralidoxime (6), which would result in unchanged or lower skin blood flow.

Atropine given in combination with pralidoxime (separate injections, same time frame) resulted in elevated T_{es} and $\bar{T}_{sk}$, by the 25th min of exercise (Table I), with a decrease in whole body and local sweating. The responses in T_{es} and $\bar{T}_{sk}$ were significantly augmented in this time frame, over those seen with atropine alone, implying a synergistic effect of the two drug actions (2). Chest and whole body sweating were slightly lower in the combined experiments, while FBF was not different from atropine treatment, which resulted in the elevated core and surface temperatures observed. Again, if the thermal gradient from the environment to the body surface is reversed, as in the case where $T_a > \bar{T}_{sk}$, this potentiation of atropine effects with 2PAM would increase the heat strain on the individual and affect performance.

One technical point can be made of this investigation which is clearly shown by Fig. 1. The use of esophageal temperature as a central indicator of thermal input offers a much more accurate and rapid response of core temperature, critical in situations when temperatures are rapidly changing. In fact, the significant changes in dT_{es}/dt with all drug treatments are not picked up by dT_{re}/dt until the drugs are combined (Table II). Therefore, during thermal transients (i.e., the early stages of exercise or recovery), the two temperatures cannot be related by a constant or a delta value. This fact must be considered when interpretations of drug effects are made from calculations of rate of change in core temperature.

We have demonstrated that atropine affects the cutaneous perfusion (arm site) as well as peripherally inhibiting eccrine (cholinergic) sweating. Specifically, FBF is enhanced with atropine and this avenue partially compensates for the sweating inhibition evident in this relatively cool environment. Pralidoxime, on the other hand, appears to also inhibit sweating and increase FBF, albeit to a much lesser extent than atropine. The regulation of internal core temperature (T_{es}) with 2PAM is not radically affected in comparison to control experiments for the dosage and environment conditions of this study, although the rate of heat loading is enhanced (Table II). It would be interesting to study and determine if this is the case in an environment where the gradient between ambient temperature and $\bar{T}_{sk}$, (e.g., $T_a - \bar{T}_{sk}$) is small or when ambient temperature actually exceeds skin temperature. Finally the combination of atropine and pralidoxime resulted in elevated heat storage during exercise, pointing to the possibility of heat injury in more severe environmental conditions.

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The opinions and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy or decision unless so distinguished by other official documentation.

Human subjects participated in these studies after giving their informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers on Research.

REFERENCES

1. Craig FN. Effects of atropine, work and heat on heart rate and sweat production in man. J. Appl. Physiol. 1952; 4:826-33.
2. Cummings EG, Craig FN, Blevins WV, Bulette CR. Physiological effects of 2PAM on exercising men in temperate and hot environments. CRD2R 3241, Edgewood Arsenal, MD, 1964.
3. Davies CTM, Brotherhood JR, ZeidiFard E. Effects of atropine and B-blockade on temperature regulation and performance during prolonged exercise. Eur. J. Appl. Physiol. 1978; 38:225-32.
4. Gaskell P. The effect of intra-arterial atropine infusions on the blood flow through the human hand and forearm. J. Physiol. (London) 1958; 142:219-32.
5. Gonzalez RR, Kolka MA. Heat exchange responses to anticholinergics. Hosp. Comm. Psych. (In Press).
6. Goodman AG, Gillman LS, Rall TW, Murad F. The pharmacological basis of therapeutics. 7th ed. New York: MacMillan Publ. Co., 1985:120-2.
7. Graichen H, Rascati R, Gonzalez RR. Automatic dew-point sensor, J. Appl. Physiol. 1982; 52:1658-60.
8. Hokanson DE, Sumner DS, Standess DE Jr. An electrically calibrated plethysmograph for direct measurement of limb blood flow. IEEE Trans. Biomed. Eng. 1975; 22:25-9.
9. Kolka MA, Holden WL, Gonzalez RR. Heat exchange following atropine injection before and after heat acclimation. J. Appl. Physiol. 1984; 56:896-9.
10. Kolka MA, Stephenson LA, Bruttig SP, Gonzalez RR. Cutaneous blood flow and local sweating during exercise after atropine. Fed. Proc. 1986; 45.
11. Mohsenin V, Gonzalez RR. Tissue pressure and plasma oncotic pressure during exercise. J. Appl. Physiol. 1984; 56:102-8.
12. Nishi Y, Gagge AP. Direct evaluation of convective heat transfer coefficient by naphthalene sublimation. J. Appl. Physiol. 1970; 28:830-8.
13. Robinson PF, McMichael PD. A comparison of the physiological responses to two modes of administration of atropine and 2PAMC1. EATR 4424, Edgewood Arsenal, MD, 1970.
14. Sato K, Sato F. Pharmacologic responsiveness of isolated single eccrine sweat glands. Am. J. Physiol. 1981; 240:R44-R51.
15. Stephenson LA, Wenger CB, O'Donovan BH, Nadel ER. Circadian rhythm in sweating and cutaneous blood flow. Am. J. Physiol. 1984; 246:R321-R324.
16. Whitney RJ. The measurement of volume changes in human limbs. J. Physiol. (London) 1953; 121:1-27.